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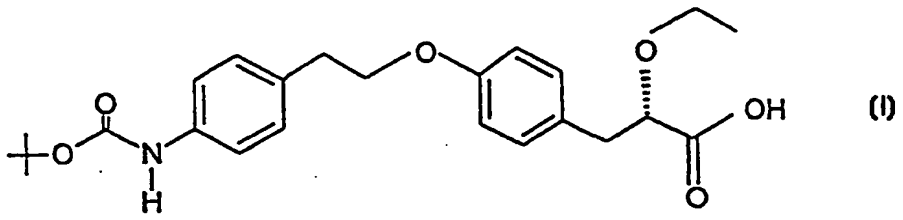

(I)

(57) Abstract

A novel compound 3–{4–[2–(4–*tert*–Butoxycarbonylaminophenyl)ethoxy]phenyl}–(S)–2–ethoxy propanoic acid having formula (I) and pharmaceutically acceptable salts, solvates, and crystalline forms thereof, a process and intermediates for its manufacture, pharmaceutical preparations containing it and the use of the compound in clinical conditions associated with insulin resistance.

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NEW 3-ARYL-2-HYDROXYPROPIONIC ACID DERIVATIVE III

Field of invention

The present invention releates to a novel 3-aryl-2-hydroxypropionic acid derivative, to a process and intermediate for preparing such a compound, having the utility in clinical conditions associated with insulin resistance, to methods for its therapeutic use and to pharmaceutical compositions containing it.

Background of the invention

Insulin resistance, defined as reduced sensitivity to the actions of insulin in the whole body or individual tissues such as skeletal muscle, myocardium, fat and liver prevail in many individuals with or without diabetes mellitus. The insulin resistance syndrome, IRS, refers to a cluster of manifestations including insulin resistance with accompanying hyperinsulinemia, possibly non insulin dependent diabetes mellitus (NIDDM); arterial hypertension; central (visceral) obesity; dyslipidemia observed as deranged lipoprotein levels typically characterized by elevated VLDL (very low density lipoproteins) and reduced HDL (high density lipoproteins) concentrations and reduced fibrinolysis.

Recent epidemiological research has documented that individuals with insulin resistance run a greatly increased risk of cardiovascular morbidity and mortality, notably suffering from myocardial infarction and stroke. In non-insulin dependent diabetes mellitus these atherosclerosis related conditions cause up to 80% of all deaths.

In clinical medicine there is at present only limited awareness of the need to increase the insulin sensitivity in IRS and thus to correct the dyslipidemia which is considered to cause the accelerated progress of atherosclerosis.

Furthermore there is at present no pharmacotherapy available to adequately correct the metabolic derangements associated with IRS. To date, the treatment of NIDDM has been focused on correction of the deranged control of carbohydrate metabolism associated with the disease. Stimulation of endogenous insulin secretion by means of secretagogues, like sulphonylureas, and if necessary administration of exogenous insulin are methods frequently used to normalize blood sugar but that will, if anything, further enhance insulin resistance and will not correct the other manifestations of IRS nor reduce cardiovascular morbidity and mortality. In addition such treatment involves a significant risk of hypoglycemia with associated complications.

Other therapeutic strategies have focused on aberrations in glucose metabolism or absorption, including biguanides, such as methformin, or glucosidase inhibitors, such as acarbose. Although these agents have been efficacious to a degree, their limited clinical effect is associated with side effects.

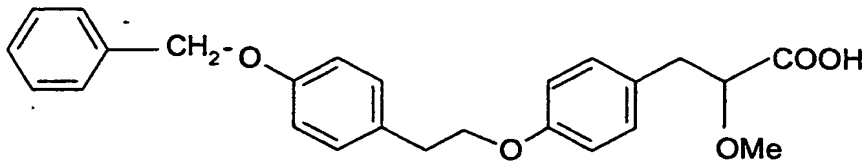
A novel therapeutic strategy involves the use of insulin sensitizing agents, such as the thiazolidinediones, which, at least in part, mediate their effects via an agonistic action on nuclear receptors. Ciglitazone is the prototype in this class. In animal models of IRS these compounds seem to correct insulin resistance and the associated hypertriglyceridaemia and hyperinsulinemia, as well as hyperglycemia in diabetes, by improving insulin sensitivity via an effect on lipid transport and handling, leading to enhanced insulin action in skeletal muscle, liver and adipose tissue.

Ciglitazone as well as later described thiazolidinediones in clinical development either have been discontinued reportedly due to unacceptable toxicity or show inadequate

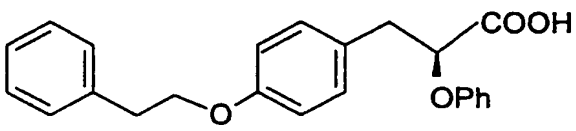
potency. Therefore there is a need for new and better compounds with insulin sensitizing properties.

Prior art

Compounds of the formula



and



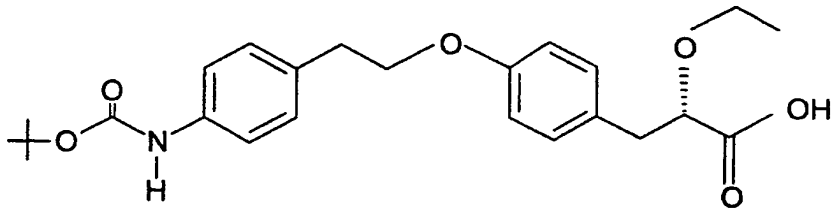
and certain derivatives thereof disclosed in US 5 306 726 and WO 91/19702 are said to be useful as hypoglycemic and hypocholesterolemic agents, and in US 5 232 945 said to be useful in the treatment of hypertension.

AU 650 429 discloses structurally related compounds, but claimed to have different properties: diuretic, antihypertensive, platelets anti-aggregating and anti-lipoxygenase properties.

EP 139 421 discloses compounds having the ability to lower blood lipid and blood sugar levels. Among these compounds is troglitazone, a compound that has reached the market for treatment of NIDDM or decreased glucose tolerance.

Description of the invention

It has now surprisingly been found that the novel compound 3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxy propanoic acid having the formula I



I

is effective in conditions associated with insulin resistance.

The invention also relates to pharmaceutically acceptable salts, solvates, such as hydrates, and crystalline forms of the compound of the formula I.

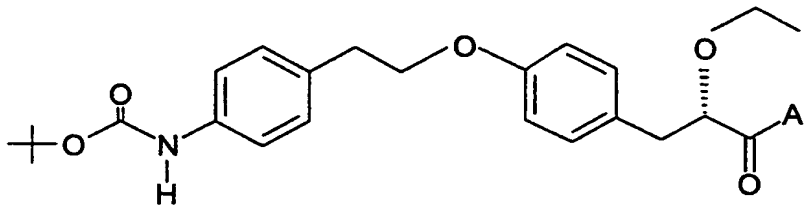
In the present specification the expression "pharmaceutically acceptable salts" is intended to define but is not limited to such salts as the alkali metal salts (e.g. sodium, lithium and potassium), alkaline earth metal salts (e.g. calcium, barium and magnesium), aluminium, zinc and bismuth salts, ammonium salts, salts with basic amino acids, such as arginine, lysine, and salts with organic amines such as ethanolamine, ethylenediamine, triethanoleamine, benzylphenethylamine, diethylamine, tromethamine, benzathine, chloroprocaine, choline, meglumine, procaine, clemizole and piperazine.

Throughout the specification and the appended claims, a given chemical formula or name shall encompass all pharmaceutically acceptable salts thereof, crystalline forms and solvates thereof such as for instance hydrates.

Methods of preparation

The compound of the invention may be prepared as outlined below according to any of methods A-H. However, the invention is not limited to these methods, the compound may also be prepared as described for structurally related compounds in the prior art.

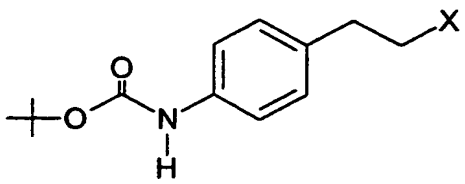
A. The compound of the formula I of the invention can be prepared by converting a compound of formula II



II

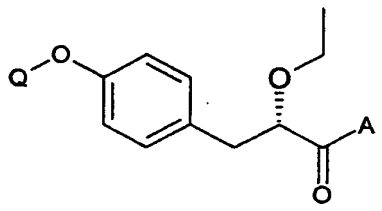
wherein A is $-OR^P$, wherein R^P is a protective group, e.g. ethyl, or A is a chiral auxiliary group, such as a chiral amine, e.g. (R)-fenylglycinol, a chiral alcohol, such as menthol or a chiral oxazolidinone, such as (S)-4-benzyl-2-oxazolidinone. The convertion can be performed as a hydrolysis which can be either acidic or basic and performed according to standard methods known to anyone skilled in the art or as described in the experimental part.

B. The compound of the formula I or the formula II wherein A is a chiral auxiliary group or $-OR^P$ and R^P is as defined above, can be prepared by reacting a compound of the formula III



III

wherein X is -OH or a leaving group such as a sulfonate or a halogen, with a compound of the formula IV



IV

wherein Q is H and A is a chiral auxiliary group, -OH or -OR^P, and R^P is as defined above. The reaction can be performed either by an alkylation reaction or a Mitsunobu reaction.

In an alkylation reaction the leaving group X can be a sulfonate such as mesylate, nosylate, tosylate, or a halogen, such as bromine or iodine. The compounds of formula III and IV, in approximately equimolar amounts or with an excess of either compound, are heated to reflux temperature in an inert solvent, such as isopropanol or acetonitrile, in the presence of a base, such as potassium carbonate or cesium carbonate.

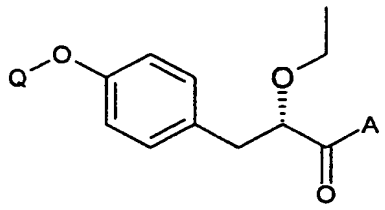
The mixture is refluxed for the necessary time, typically between 0.5 h to 24 h, the work up procedure usually includes filtration, for removal of solid salt, evaporation, neutralisation (when A = -OH) and extraction with water and an organic solvent such as dichloromethane, ethyl acetate, or diethyl ether. The crude product is purified if desired e.g. by recrystallization or by standard chromatographic methods.

The Mitsunobu reaction can be carried out according to standard methods or as described in for example Tsunoda T., Yamamiaya Y., Ito S., Tetrahedron Letters, 34, 1639-1642 (1993) or O. Mitsunobu, Synthesis, 1981, p.1. When using a Mitsunobu reaction A can not be -OH.

In a typical Mitsunobu reaction a compound of formula III, wherein the group X is a hydroxyl group, and a compound of formula IV are mixed, in approximately equimolar amounts or with an excess of either compound, in an inert solvent, such as chloroform, dichloromethane, or tetrahydrofuran. A slight molar excess, 1-4 equivalents, of an azodicarboxylate, such as DEAD or ADDP and a phosphine (1-4 equivalents), such as tributylphosphine or triphenylphosphine are added and the reaction is stirred at a temperature high enough - for example room temperature - and a time long enough (1-24 hours) to obtain product, which can be worked up with standard literature methods and if desired purified, e.g. by standard chromatographic methods.

The compound of formula III can be prepared by standard procedures known to anyone skilled in the art, from commercially available starting materials or as described in the experimental section.

The compound of formula IV wherein Q is H and A is a chiral auxiliary group, -OH or $-OR^P$, wherein R^P is as defined above, can be prepared as described below in the experimental part, or by converting a compound of formula IV

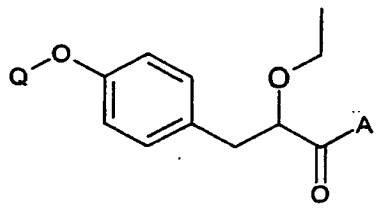


IV

wherein Q is R^Q, wherein R^Q is a protective group, e.g. benzyl, and A is a chiral auxiliary group, -OH or $-OR^P$, wherein R^P is as defined above.

C. The compound of formula II ,wherein A is a chiral auxiliary group, and the compound of formula IV, wherein A is a chiral auxiliary group and Q is hydrogen or R^Q, wherein R^Q

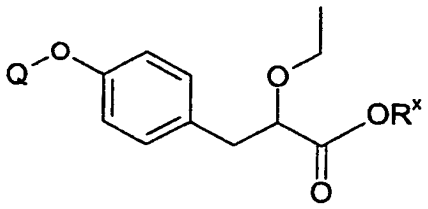
is as defined above and, can be prepared by diastereoisomeric separation of the compound of the formula V



V

wherein A is a chiral auxiliary group, Q is hydrogen, $-CH_2CH_2Ph$-4-$NHCOO^tBu$ or R^q, wherein R^q is as defined above. The separation of the diastereomers can be performed either by crystallization or by chromatography. The chromatographic separation can be performed as described in the experimental part.

The compound of formula V wherein A is a chiral auxiliary group, Q is hydrogen, $-CH_2CH_2Ph$-4-$NHCOO^tBu$ or R^q, wherein R^q is as defined above, can be prepared by converting a compound of formula VI



VI

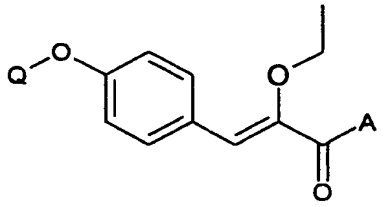
wherein Q is hydrogen, $-CH_2CH_2Ph$-4-$NHCOO^tBu$ or R^q and R^x is hydrogen or R^p, wherein R^q and R^p are as defined above, for example by reacting it with a chiral amine or a chiral alcohol.

The compound of formula V when A is a chiral amine can be prepared by reacting a compound of formula VI with a chiral amine such as (R)-phenyl glycinol for example in the presence of a peptide coupling system (e.g. EDC, DCC, HBTU, TBTU, PyBop or

oxalylchloride in DMF), an appropriate base (e.g. pyridine, DMAP, TEA or DiPEA) and a suitable organic solvent (e.g. dichloromethane, acetonitrile or DMF) in accordance to methods well known to those skilled in the art or as described in the examples.

The compound of formula V when A is a chiral alcohol can be prepared in the same way using a chiral alcohol, such as menthol, instead of a chiral amine, or by the mix-anhydride method with pivaloyl chloride and the lithium salt of the chiral alcohol.

The compound of formula V wherein A is a chiral auxiliary group and Q is hydrogen, $-CH_2CH_2Ph$-4-$NHCOO^tBu$ or R^q, wherein R^q is as defined above, and the compound of formula VI, wherein Q is hydrogen, $-CH_2CH_2Ph$-4-$NHCOO^tBu$ or R^q and R^x is hydrogen or R^p, wherein R^q and R^p are as defined above, can be prepared by reduction of a compound of formula VII



VII

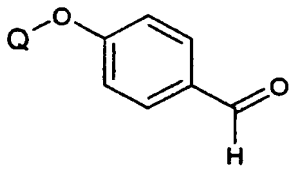
wherein A is a chiral auxiliary group, -OH, or $-OR^p$, wherein R^p is as defined above and Q is hydrogen, $-CH_2CH_2Ph$-4-$NHCOO^tBu$ or R^q, wherein R^q is as defined above, and if desired followed by removal of protecting groups.

The reduction of the olefin may be carried out using a wide variety of reducing methods known to reduce carbon-carbon double bonds, such as catalytic hydrogenation in the presence of an appropriate catalyst, or hydrogen transfer reagents such as diethyl-2,5-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate.

The catalytic hydrogenation can be performed in alcohol, cellosolves, protic polar organic solvents, ethers, lower alifatic acids, and particularly in methanol, ethanol, methoxyethanol, dimethylformamide, tetrahydrofuran, dioxane, dimetoxyethane, ethyl acetate or acetic acid either used alone or in mixture. Examples of the catalysts used include palladium black, palladium on charcoal, platinum oxide or Wilkinson's catalyst. This reaction can be performed at different temperatures and pressures depending on the reactivity of the aimed reaction.

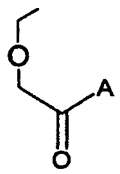
In case of hydrogen transfer reaction with diethyl-2,5-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate the reaction can be conducted by mixing equimolar amounts of reactants and warming the mixture to melting (140-250°C) under inert atmosphere or under vacuum.

The compound of formula VII wherein A is a chiral auxiliary group, -OH, or -OR^P, wherein R^P is as defined above and Q is hydrogen, -CH_2CH_2Ph-4-NHCOO^tBu or R^q, wherein R^q is as defined above, can be prepared by a condensation reaction, such as a Knoevenagel or Wittig type reaction, of a carbonyl compound of the formula VIII



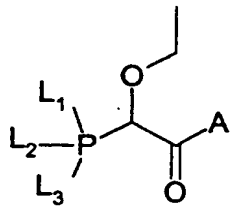
VIII

wherein Q is hydrogen, -CH_2CH_2Ph-4-NHCOO^tBu or R^q, wherein R^q is as defined above, with a compound of the formula IX



IX

in which formula A is a chiral auxiliary group, -OH, -OR^P, wherein R^P is as defined above, or the formula X



X

in which A is a chiral auxiliary group, or -OR^P, wherein R^P is as defined above, $L^1 = L^2 = L^3$ are phenyl or $L^1 = L^2$ are Oalkyl and L^3 is = O, and, if desired, followed by removal of protecting groups, by an arylation reaction as described in for example Cacchi S., Ciattini P. G., Morera E., Ortar G., Tetrahedron Letters, 28 (28) 1987, pp 3039-3042.

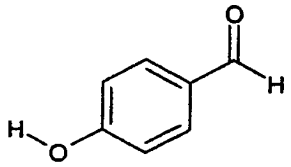
In the condensation step, approximately equimolar amounts of reactants are mixed in the presence of a base, to provide the olefin compound. This step may be carried out in the presence of an inert solvent or in the absence of a solvent at a temperature between -20°C and the melting point for the mixture. It might be necessary to add a dehydrating agent in order to obtain the olefinic compound.

In a typical such reaction the compounds of formula VIII and formula IX are mixed in a solvent such as tetrahydrofuran. Anhydrous potassium *tert*-butoxide is slowly added at low temperature i.e. -20°C. The reaction is quenched with acetic acid. The crude product is isolated, redissolved in toluene and refluxed with p-toluenesulfonic acid in a Dean-Stark apparatus. The solution is cooled and the product is isolated and purified according to standard methods (see Groger T., Waldmann E., Monatsh Chem 89, 1958, p 370).

The condensation step could also be performed as a Wittig-type reaction (see for example Comprehensive Organic Synthesis vol. 1 p. 755-781 Pergamon Press) or as described in the experimental part.

In a typical such reaction, approximately equimolar amounts of reactants of formula VIII and formula X, are stirred in the presence of a base such as tetramethylguanidine or potassium carbonate in a 1-5 fold molar excess. This step may be carried out in the presence of an inert solvent such as dichloromethane or acetonitrile and at a suitable temperature (-10° C + 60° C) and at a time long enough.

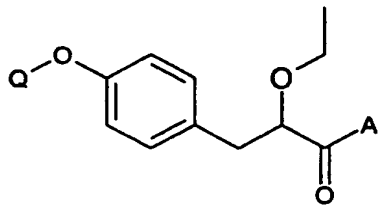
The compound of the formula VIII when Q is $-CH_2CH_2Ph$-4-$NHCOO^tBu$ can be prepared by coupling a compound of the formula III wherein X is -OH or a leaving group such as a sulfonate or a halogen, with a compound of the formula XI



XI

When X is a leaving group such as a sulfonate or a halogen, the reaction may be performed as an alkylation reaction and when X is -OH, as a Mitsunobu reaction as described above.

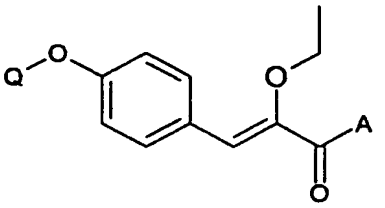
D. The compound of formula I or formula II wherein A is $-OR^P$ and R^P is as defined above and the compound of formula IV wherein A is -OH or $-OR^P$ and Q is H or R^q, wherein R^P and R^q are as defined above can be prepared by enantiomeric separation, such as chiral chromatography of the compound of the formula V



V

wherein A is -OH or -OR^P, Q is H, -CH_2CH_2Ph-4-NHCOO^tBu or R^Q wherein R^P and R^Q are as defined above.

E. The compound of the formula I or the formula II wherein A is a chiral auxiliary group, or -OR^P, wherein R^P is as defined above, and the compound of formula IV wherein A is a chiral auxiliary group, -OH, or -OR^P, wherein R^P is as defined above and Q is hydrogen or R^Q, wherein R^Q is as defined above and, can be prepared by asymmetric reduction of a compound of the formula VII



VII

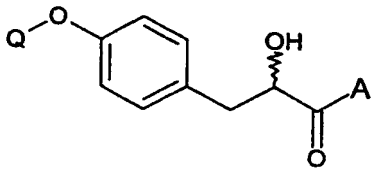
wherein A is a chiral auxiliary group, -OH, or -OR^P, wherein R^P is as defined above and Q is hydrogen, -CH_2CH_2Ph-4-NHCOO^tBu or R^Q, wherein R^Q is as defined above.

The asymmetric reduction can be carried out using a wide variety of reducing methods wich are known to reduce carbon-carbon double bonds such as catalytic hydrogenation in the presence of an appropriate chiral catalyst such as Rh-BINAP or [Et-DuPHOS-Rh(COD)] or catalytic hydrogenation with an appropriate catalyst, such as palladium on charcoal using the chiral auxiliary group to induce the asymmetry.

The catalytic hydrogenation can be carried out in a wide variety of solvents, such as alcohol, cellosolves, protic polar organic solvents, ethers, lower alifatic acids, and

particularly in methanol, ethanol, methoxyethanol, dimethylformamide, tetrahydrofuran, dioxane, dimetoxyethane, ethyl acetate or acetic acid, either used alone or in a mixture. The reaction can proceed at different temperatures and pressures depending on the reactivity of the aimed reaction.

F. The compound of the formula I or the formula II, wherein A is a chiral auxiliary group, or $-OR^P$, wherein R^P is as defined above, and the compound of formula IV wherein A is a chiral auxiliary group, -OH, or $-OR^P$, wherein R^P is as defined above and Q is hydrogen or R^Q, wherein R^Q is as defined above, can be prepared by converting a compound of the formula XII



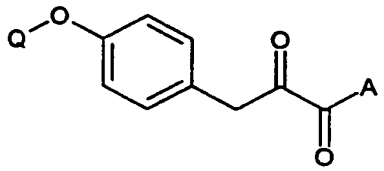
XII

wherein A is a chiral auxiliary group, -OH, or $-OR^P$, wherein R^P is as defined above, and Q is hydrogen, $-CH_2CH_2Ph$-4-$NHCOO^tBu$ or R^Q, wherein R^Q is as defined above, with the required stereochemistry, dependent on the reaction conditions used.

The reaction may be carried out as an alkylation reaction, using a variety of alkylating agents, such as ethyl halide or diethyl sulfate (see for example Benedict D.R., Bianchi T.A., Cate L.A., Synthesis (1979), pp. 428-429, Barluenga J., Alonso-Cires L., Campos P.J., Asensio G., Synthesis, 1983, p. 53-55, Bull Chem Soc Jpn, 1986, 59, 2481, S. Patai, The Chemistry of the Ether Linkage, Wiley-Interscience NY, 1967, 445-498 or Survey of Organic Synthesis vol 1, Wiley-Interscience 1970, NY, p. 285-328).

The compound of formula XII wherein A is a chiral auxiliary group, -OH, or $-OR^P$, wherein R^P is as defined above, and Q is hydrogen, $-CH_2CH_2Ph$-4-$NHCOO^tBu$ or R^Q,

wherein R^q is as defined above, can be prepared by asymmetric reduction of a compound of the formula XIII



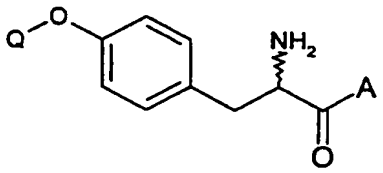
XIII

wherein A is a chiral auxiliary group, -OH, or -OR^p, wherein R^p is as defined above, and Q is hydrogen, -CH_2CH_2Ph-4-NHCOO^{t}Bu or R^q, wherein R^q is as defined above.

The asymmetric reduction may be performed by using a wide variety of reducing methods which are known to reduce ketones enantioselectively (see Flynn G.A., Beight D.W., Tetrahedron Letters, 29(4), 1988, pp. 423-426).

The compound of formula XII wherein A is a chiral auxiliary group and Q is hydrogen, -CH_2CH_2Ph-4-NHCOO^{t}Bu or R^q, wherein R^q is as defined above, may also be prepared by induced chiral reduction of a compound of formula XIII, wherein A is a chiral auxiliary group and Q is hydrogen, -CH_2CH_2Ph-4-NHCOO^{t}Bu or R^q, wherein R^q is as defined above (see Xiang Y.B.,.Snow K., Belley M., J. Org. Chem., 1993, 58, pp 993-994).

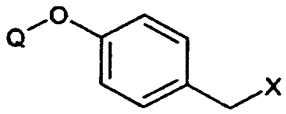
The compound of formula XII, wherein A is a chiral auxiliary group, -OH or -OR^p, wherein R^p is as defined above, and Q is hydrogen, -CH_2CH_2Ph-4-NHCOO^{t}Bu or R^q, wherein R^q is as defined above, can be prepared by converting a compound of the formula XIV



XIV

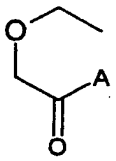
wherein A is a chiral auxiliary group, -OH or -OR^P, wherein R^P is as defined above, and Q is hydrogen, -CH_2CH_2Ph-4-NHCOO^tBu or R^q, wherein R^q is as defined above, with the required stereochemistry, dependent on the reaction conditions used (see for example K. Koga, C.C. Wu and S. Yamada, Tetrahedron Letters, no. 25, 1971, p 2283-2286 , Kunz H., Lerchen H-G., TetrahedronLetters, 28 (17) 1987, pp.1873-1876).

G. The compound of formula II, wherein A is a chiral auxiliary group, and the compound of formula IV wherein A is a chiral auxiliary group and Q is R^q, wherein R^q is as defined above, can be prepared by reacting a compound of formula XV



XV

wherein X is a leaving group, such as a halogen or a sulfonate, and Q is -CH_2CH_2Ph-4-NHCOO^tBu or R^q, wherein R^q is as defined above, with a compound of the formula IX



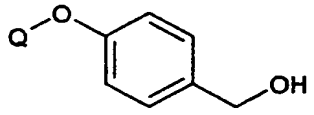
IX

wherein A is a chiral auxiliary group.

In the alkylation step the compound of formula XV is reacted with a compound of formula IX in the presence of one or more bases such as potassium carbonate, triethylbenzylammonium chloride, sodium hydride, LDA, butyllithium or LHMDS in a reaction inert solvent such as acetonitrile, DMF or dichloromethane at a suitable temperature and time. The reaction can be carried out using standard methods known in the

litterature. (see for example Pearsson W.H., Cheng M.C., J. Org. Chem., 51 (19) 1986, 3746-3748, Myers A.G., Yang B.H., Gleason J.L., J. Am. Chem. Soc. 1994, 116, pp 9361-9362, Negrete G.R., Konopelski J.P., Tetrahedron Assymetry, 2, 2, pp. 105-108, 1991, Davies S.G., Sanganee H.J., Tetrahedron Assymetry, 6, 3, pp. 671-674, 1995, Hulin B., Newton L.S., Lewis D.M., Genereux P.E., Gibbs E.M., Clark D.A. J. Med.Chem. 39, 3897-3907 (1996) and Savignac M., Durand J-O, Genet J-P, Tetrahedron Assymetry, 5, 4, pp.717-722, 1994).

The compound of formula XV wherein X is a leaving group, such as a halogen or a sulfonate, and Q is -CH_2CH_2Ph-4-NHCOO^{t}Bu or R^q, wherein R^q is as defined above, can be prepared from a compound of formula XVI



XVI

wherein Q is -CH_2CH_2Ph-4-NHCOO^{t}Bu or R^q, wherein R^q is as defined above, using standard methods known to anyone skilled in the art.

The compound of formula XVI wherein Q is - CH_2CH_2Ph-4-NHCOO^{t}Bu or R^q , wherein R^q is as defined above, can be prepared by reduction of a compound of formula VIII, wherein Q is -CH_2CH_2Ph-4-NHCOO^{t}Bu or R^q, wherein R^q is as defined above, by standard methods known to anyone skilled in the art.

H. The compound of the invention of formula I and the compound of formula IV, wherein A is -OH and Q is hydrogen or R^q, wherein R^q is as defined above, can be prepared by resolution of the racemate thereof and, if desired, followed by neutralization.
The resolution can be performed by separative crystallization of a salt consisting of the racemate of, either the compound of the invention of formula I, or the compound of formula IV, and a chiral base, such as quinine, in an inert solvent such as ethyl acetate or

toluene (see for example Duhamel P., Duhamel L., Danvy D., Plaquevent J. C., Giros B., Gros C., Schwartz J.C., Lecomte J.M., US 5136076, Stephani R., Cesare V., J. Chem. Ed., 10, 1997, p. 1226 and Yamamoto M., Hayashi M., Masaki M., Nohira H., Tetrahedron Assymetry, 2, 6, pp. 403-406, 1991).

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques.

Persons skilled in the art will appreciate that, in order to obtain the compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in different order, and/or the individual reactions may be performed at different stage in the overall route (i.e. chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

In any of the preceeding methods of preparation A-H, where necessary, hydroxy, amino or other reactive groups may be protected using a protecting group, R^p or R^q as described in the standard text "Protective groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts. The protecting group R^p or R^q may also be a resin, such as Wang resin or 2-chlorotrityl chloride resin. The protection and deprotection of functional groups may take place before or after any of the reaction steps described hereinbefore. Protecting groups may be removed in accordance to techniques which are well known to those skilled in the art.

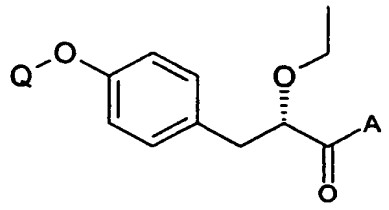
The expression "inert solvent" refers to a solvent which does not react with the starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

Unless otherwise stated or indicated the term chiral auxiliary group denotes a chiral group, such as a chiral alcohol or amine, for instance (-)-menthol, (+)-isomenthol, (-)-norneol,

(R)-2-phenyl glycinol, (S)-2-phenyl glycinol, (R)-4-phenyl-2-oxazolidinone or (S)-4-benzyl-2-oxazolidinone, which chiral group when connected to a carbonyl group can easily be cleaved to the corresponding acid.

Intermediates

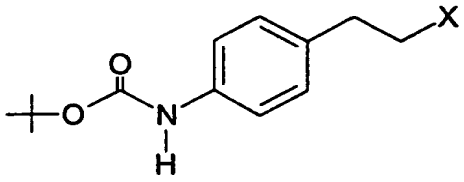
a) When preparing the compound of the formula I of the invention an intermediate of the formula IV



IV

wherein Q is hydrogen and A is -OH or -OR^P, wherein R^P is a protective group, e.g. ethyl, or A is a chiral auxiliary group, such as a chiral amine, e.g. (R)-fenylglycinol, or a chiral alcohol such as menthol, or a chiral oxazolidinone, such as (S)-4-benzyl-2-oxazolidinone, is particularly useful. It is prepared as described above. Under the same heading its use as intermediate for the preparation of the end compound of the invention is described.

b) When preparing the compound of the formula I of the invention an intermediate of the formula III



III

wherein X is -OH or a leaving group, such as a sulfonate or a halogen, is particularly useful. It is prepared as described above. Under the same heading its use as intermediate for the preparation of the end product of the invention is described.

Pharmaceutical preparations

The compound of the invention will normally be administered via the oral, parenteral, intravenous, buccal, rectal, vaginal, transdemal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free acid, or a pharmaceutical acceptable organic or inorganic base addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

The compound of the invention may also be combined with other therapeutic agents which are useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidemias, dyslipidemias, diabetes and obesity.

Suitable daily doses of the compound of the invention in therapeutical treatment of humans are about 0.005-5 mg/kg body weight, preferably 0.01-0.5 mg/kg body weight.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including the compound of the invention, or pharmaceutically acceptable derivatives thereof, in optional admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

Pharmacological properties

The present compound of formula (I) will be adapted for prophylaxis and/or treatment of clinical conditions associated with reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders. These clinical conditions will include, but will not be limited to, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia (non insulin dependent diabetes mellitus (NIDDM)) and the dyslipidaemia (plasma lipoprotein disturbances) characteristically appearing with insulin resistance. This

dyslipidaemia, also known as the atherogenic lipoprotein profile of phenotype B, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoproteins (VLDL) triglycerides, low high density lipoproteins (HDL) cholesterol and the presence of small, dense, low density lipoproteins (LDL). Treatment with the present compound is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis. These cardiovascular disease conditions include macro-angiophaties causing myocardial infarction, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of their insulin sensitizing effect the compound of formula (I) is also expected to reduce the progress of clinical conditions associated with chronic hyperglycaemia in diabetes like the micro-angiophaties causing renal disease and retinal damage. Furthermore the compound may be useful in treatment of various conditions outside the cardiovascular system associated with insulin resistance like the polycystic ovarian syndrome. The compound of the invention is a non-toxic insulin sensitizing agent with surprisingly good therapeutic effect and pharmacokinetic properties and without undesirable weight gain.

General Experimental Procedures

^{1}H NMR and ^{13}C NMR measurements were performed on a BRUKER ACP 300 and Varian UNITY plus 400 and 500 spectrometers, operating at ^{1}H frequencies of 300, 400 and 500 MHz respectively, and at ^{13}C frequencies of 75, 100 and 125 MHz respectively.

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal standard.

Example 1. 3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid.

a) 3-(4-Benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester

Tetramethylguanidine (33 g; 0.286 mole) was added to a solution of 4-benzyloxybenzaldehyde (59.1 g; 0.278 mole) and 101.8 g; 0.237 mole) (1,2-dietoxy-2-oxyethyl) (triphenyl) phosphonium chloride in dichloromethane (600 ml) at 0°C. After stirring at room temperature over night, the solvent was evaporated *in vacuo*. The residue was dissolved in diethyl ether, insoluble material was filtered off and the filtrate was evaporated. The residue was stirred over night with sodium bisulfite (saturated water solution) and diethyl ether. The solid material was filtered off, the filtrate was extracted with diethyl ether, dried (magnesium sulfate) and the solvent was evaporated *in vacuo*. Purification of the crude product by flash chromatography and crystallization in isopropanol gave 66.8 g (yield 86.3 %) of 3-(4-benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester.

^{13}C-NMR (125 MHz; $CDCl_3$): δ 14.4, 15.6, 61.0, 67.5, 70.0, 114.8, 124.0, 126.7, 127.5, 128.1, 128.6, 131.7, 136.7, 143.1, 159.2, 165.0.

(b) 2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester

3-(4-Benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester (62 g; 0.19 mole) was hydrogenated in ethyl acetate (400 ml) at atmospheric pressure using Pd/C (10 %) as catalyst. The mixture was filtered through celite and evaporated *in vacuo* to give 45.6 g (yield 100 %) of 2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 1.23 (t, 3H, J=7 Hz), 2.95 (d, 2H, J=6.6 Hz), 3.35-3.42 (m, 1H), 3.58-3.64 (m, 1H), 4.0 (t, 1H, J=6.6 Hz), 4.17 (q, 2H, J=7 Hz), 5.97 (s, 1 OH), 6.74 (dm, 2H, J=8.5 Hz, unresolved), 7.08 (dm, 2H, J=8.5 Hz, unresolved).

^{13}C-NMR (125 MHz; $CDCl_3$): δ 14.0, 14.8, 38.3, 61.0, 66.1, 80.3, 115.1, 128.2, 130.3, 154.8, 173.0.

(c) 4-(2-Hydroxyethyl)phenylcarbamic acid *tert*-butyl ester

Di-*tert*-Butyl dicarbonate (7.95 g; 36 mmole) was added to a mixture of p-aminophenethyl alcohol (5 g; 36 mmole) in tetrahydrofuran at 0° C. After stirring at room temperature over night, the solvent was evaporated *in vacuo* to give 8 g (yield 94 %) of 4-(2-hydroxyethyl)phenylcarbamic acid tert-butyl ester.

^{1}H-NMR (400 MHz; DMSO-d_6): δ 1,5 (s, 9H), 2,65 (dd, 2H), 3,55 (dd, 2H), 4,6 (bs, 1 OH), 7,1 (unresolved, 2H), 7,35 (unresolved, 2H), 9,1 (s, 1 NH).
^{13}C-NMR (100 MHz; DMSO-d_6): δ 28.3, 38.6, 62.5, 78.9, 118.3, 129.1, 133.2, 136.6, 153.0.

(d) 3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester

4-(2-Hydroxyethyl)phenylcarbamic acid *tert*-butyl ester (1.03 g; 4.34 mmole) and 2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester (1.03 g; 4.34 mmole) were dissolved in dichloromethane under argon at room temperature. Azodicarbonyl dipiperidine (1.65 g; 6.5 mmole) and thereafter triphenylphosphine (1.37 g; 5.2 mmole) were added. After stirring at room temperature for 6 hours the solvent was evaporated *in vacuo*. Purification by chromatography on silica gel using heptan:ethyl acetate (2:1) as eluant gave 1.78 g (yield 89%) of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]-phenyl}-2-ethoxypropanoic acid ethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.17 (t, 3H, J=7 Hz), 1.23 (t, 3H, J=7 Hz), 1.53 (s, 9H), 2.94-2.97 (m, 2H), 3.03 (t, 2H, J=7.1 Hz), 3.31-3.40 (m, 1H), 3.56-3.65 (m, 1H), 3.95-4.0 (m, 1 H), 4.11 (t, 2H, J=7.1 Hz), 4.17 (q, 2H, J=7 Hz), 6.60 (s, 1NH), 6.81 (dm, 2H, J=8.3 Hz, unresolved), 7.15 (dm, 2H, J=8.3 Hz, unresolved), 7.20 (dm, 2H, J=8.3 Hz, unresolved), 7.31 (dm, 2H, J=8.3 Hz, unresolved).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.1, 15.0, 28.3, 35.0, 38.4, 60.7, 66.1, 68.6, 80.26, 80.32, 114.3, 118.7, 128.2, 129.4, 130.3, 132.8, 136.7, 152.8, 157.5, 172.4.

(e) 3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid

Lithium hydroxide hydrate (77 mg; 1.85 mmole) in water (5.5 ml) was slowly added to a solution of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid ethyl ester (0.77 g; 1.68 mmole) in tetrahydrofuran (7.6 ml). After stirring at room temperature for 4 hours the reaction mixture was kept in a freezer for 4 days. Tetrahydrofuran was removed by evaporation *in vacuo*. More water was added and the mixture was acidified with hydrochloric acid to pH 1. The product was extracted with ethyl acetate, washed twice with water, dried (sodium sulfate), filtered and the solvent was evaporated *in vacuo* to give 0.716 g of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)-ethoxy]phenyl}-2-ethoxypropanoic acid.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.18 (t, 3H, J=7 Hz), 1.54 (s, 9H), 2.93-3.10 (m, 4H), 3.36-3.45 (m, 1H), 3.60-3.69 (m, 1H), 4.02-4.07 (m, 1 H), 4.12 (t, 2H, J=7 Hz), 6.83 (dm, 2H, J=8.8 Hz, unresolved), 7.15-7.23 (m, 4H), 7.27-7.34 (m, 2H), 10.28 (bs, 1H).
^{13}C-NMR (100 MHz; $CDCl_3$): δ 15.0, 28.3, 35.2, 38.0, 66.7, 68.8, 79.9, 80.7, 114.6, 119.1, 129.0, 129.4, 130.4, 133.1, 136.8, 153.2, 157.8, 175.3.

(f) 3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid.

The enantiomers of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-2-ethoxypropanoic acid was separated with chiral preparativ HPLC (Chiralpak AD 250x20 mm) using heptane, isopropanol and trifluoroacetic acid (80/20/0.5) as mobil phase giving 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid as a pure enantiomer.

^{1}H-NMR (600 MHz; $CDCl_3$): δ 1.17 (t, 3H), 1.51 (s, 9H), 2.93 (dd, 1H), 3.02 (t, 2H), 3.07 (dd, 1H), 3.42-3.47 (m, 1H), 3.55-3.6 (m, 1H), 4.04 (dd, 1H), 4.1 (t, 2H), 6.5 (bs, 1H), 6.8 (d, 2H), 7.13 (d, 2H), 7.19 (d, 2H), 7.28 (d, 2H).

^{13}C-NMR (100 MHz; CD_3OD): δ 15.3, 28.7, 36.1, 39.3, 67.1, 69.9, 80.7, 81.3, 115.4, 120.0, 130.3, 130.7, 131.4, 134.2, 138.8, 155.4, 159.1, 176.0.

Example 2: 3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid.

a) 3-(4-Benzyloxyphenyl)-2-ethoxypropanoic acid ethyl ester

3-(4-Benzyloxyphenyl)-2-ethoxyacrylic acid ethyl ester (described in Example 1a) (0.5 g; 1.5 mmole) was hydrogenated at atmospheric pressure using rhodium on charcoal as catalyst (5%, 50 mg) in methanol (20 ml). The crude product was purified by chromatography using heptane:ethyl acetate (5:1) as eluent to give 50 mg (yield 10%) of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid ethyl ester.

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.47-7.30 (m, 5H), 7.17 (d, J=8.8, 2H), 6.91 (d, J=8.8 Hz, 2H), 5.06 (s, 2H), 4.17 (q, J=7.2 Hz, 2H), 3.98 (t, J=6.6 Hz, 1H), 3.61 (dq, J=8.9 and 6.8 Hz, 1H), 3.36 (dq, J=8.9 and 6.8 Hz, 1H), 2.97 (d, J=6.6 Hz, 2H), 1.22 (t, J=7.2 Hz, 3H), 1.18 (t, J=6.8 Hz, 3H).
^{13}C NMR (75 MHz; $CDCl_3$): δ 172.6, 157.6, 137.1, 130.4, 129.5, 128.6, 127.9, 127.5, 114.6, 80.4, 70.0, 66.2, 60.8, 38.5, 15.1, 14.2.

b) 3-(4-Benzyloxyphenyl)-2-ethoxypropanoic acid

Lithium hydroxide hydrate (7.4 g; 177 mmole) dissolved in water (150 ml) was added to a solution of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid ethyl ester (23.25 g; 70.8 mmole) in dioxan (150 ml). After stirring at room temperature over night dioxan was

evaporated *in vacuo*, water was added and the mixture was washed with diethyl ether. The water phase was acidified with hydrochloric acid (1 M) and the crude product was extracted with ethyl acetate, washed with water and brine, dried and the solvent was evaporated *in vacuo* to give 21.1 g (yield 99.2 %) of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid.

^{1}H NMR (300 MHz; $CDCl_3$): δ 1.15 (t, 3H), 2.9-3.1 (m, 2H), 3.35-3.45 (m, 1H), 3.6-3.7 (m, 1H), 3.95-3.41 (m, 1H), 5.05 (s, 2H), 6.95 (d, 2H), 7.2 (d, 2H), 7.25-7.5 (m, 5H).
^{13}C NMR (75 MHz; $CDCl_3$): δ 15.0, 38.1, 66.6, 70.0, 79.9, 114.7, 127.5, 128.0, 128.6, 129.3, 130.5, 137.1, 157.7, 176.3.

c) 3-(4-Benzyloxyphenyl)-(S)-2-ethoxy-N-(2-hydroxy-(R)-1-phenylethyl)propanoic amide

EDC (2.03 g; 10.61 mmole), diisopropylethylamine (1.84 ml, 10.61 mmole) and HOBt x H_2O (1.43 g; 10.61 mmole) were added to a solution of 3-(4-benzyloxyphenyl)-2-ethoxypropanoic acid (2.92 g, 9.74 mmole) in dry dichloromethane (30 ml) on an ice-bath. After 30 minutes the ice-bath was removed and (R)-phenylglycinol (1.46 g, 10.61 mmole) was added. After stirring at room temperature over night ethyl acetate (100 ml) was added and the solution was washed with potassium hydrogensulfate (1 M), saturated sodium bicarbonate solution, sodium carbonate solution and brine. The organic phase was dried (sodium sulfate), filtered and the solvent was evaporated *in vacuo*. The crude product was purified by chromatography on silica gel using ethyl acetate:heptan to give 1.5 g (yield 37 %) of 3-(4-benzyloxyphenyl)-(S)-2-ethoxy-*N*-(2-hydroxy-(R)-1-phenylethyl)propanoic amide and 1.25 g (yield 31 %) of 3-(4-benzyloxyphenyl)-(R)-2-ethoxy-*N*-(2-hydroxy-(R)-1-phenylethyl)propanoic amide.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.43-7.27 (m, 8H), 7.22 (d, J=8.3 Hz, 4H), 7.13 (d, NH, J=7.8 Hz, 1H), 6.96 (d, J=8.3 Hz, 1H), 5.08 (s, 2H), 5.01 (m, 1H), 3.99 (dd, J=6.8 and 3.9 Hz, 1H), 3.69 (m, 2H), 3.50 (q, J=6.8 Hz, 2H), 3.15 (dd,

J=14.2 and 3.9 Hz, 1H), 2.97 (dd, J=14.2 and 6.8 Hz, 1H), 2.94 (m, OH, 1H), 1.16 (t, J=6.8 Hz, 3H).

^{13}C NMR (100 MHz; $CDCl_3$): δ 172.3, 157.5, 138.9, 137.0, 130.7, 129.4, 128.6, 128.4, 127.7, 127.6, 127.3, 126.5, 114.4, 81.0, 69.8, 66.3, 66.0, 55.3, 37.8, 15.1.

d) 3-(4-Benzyloxyphenyl)-(S)-2-ethoxypropanoic acid

3-(4-Benzyloxyphenyl)-(S)-2-ethoxy-*N*-(2-hydroxy-(R)-1-phenylethyl)propanoic amide (8.9 g; 21.22 mmole) was hydrolyzed with concentrated sulfuric acid (27 ml) in water (104 ml) and dioxane (104 ml) at 90° C for 5 hours. The reaction mixture was poured onto water (220 ml) and extracted with ethyl acetate. The organic phase was washed with brine, dried (sodium sulfate) and the solvent was evaporated *in vacuo* to give 6.85 g of a mixture of 3-(4-benzyloxyphenyl)-2-(S)-ethoxypropanoic acid and (S)-2-ethoxy-3-(4-hydroxyphenyl)-propanoic acid, which was used without further purification.

^{1}H NMR (400 MHz; $CDCl_3$): δ 7.47-7.30 (m, 5H), 7.19 (d, J=8.8, 2H), 6.93 (d, J=8.8 Hz, 2H), 5.10 (s, 2H), 4.06 (dd, J=7.8 and 4.4 Hz, 1H), 3.64 (dq, J=9.8 and 6.8 Hz, 1H), 3.44 (dq, J=9.8 and 6.8 Hz, 1H), 3.09 (dd, J=14.2 and 4.4 Hz, 1H), 2.98 (dd, J=14.2 and 7.8 Hz, 1H), 1.19 (t, J=6.8 Hz, 3H).

e) 3-(4-Benzyloxyphenyl)-(S)-2-ethoxypropanoic acid ethyl ester

Hydrogen chloride (g) was bubbled through a solution of 3-(4-benzyloxyphenyl)-2-(S)-ethoxypropanoic acid (6.85 g) in ethanol (400 ml). Thionyl chloride (2 ml, 27.4 mmole) was slowly added and the reaction mixture was refluxed for 2 hours. The solvent was evaporated *in vacuo* to give 8 g of a mixture of 3-(4-benzyloxyphenyl)-(S)-2-ethoxypropanoic acid ethyl ester and (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester which was used without further purification.

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.47-7.30 (m, 5H), 7.17 (d, J=8.8, 2H), 6.91 (d, J=8.8 Hz, 2H), 5.06 (s, 2H), 4.17 (q, J=7.2 Hz, 2H), 3.98 (t, J=6.6 Hz, 1H), 3.61 (dq, J=8.9 and 6.8 Hz, 1H), 3.36 (dq, J=8.9 and 6.8 Hz, 1H), 2.97 (d, J=6.6 Hz, 2H), 1.22 (t, J=7.2 Hz, 3H), 1.18 (t, J=6.8 Hz, 3H).

^{13}C NMR (75 MHz; $CDCl_3$): δ 172.6, 157.6, 137.1, 130.4, 129.5, 128.6, 127.9, 127.5, 114.6, 80.4, 70.0, 66.2, 60.8, 38.5, 15.1, 14.2.

f) (S)-2-Ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester

3-(4-Benzyloxyphenyl)-(S)-2-ethoxypropanoic acid ethyl ester was hydrogenated at atmospheric pressure for 2 hours in ethyl acetate using Pd/C as catalyst. Purification by chromatography on silica gel using toluen:ethyl acetate as eluant gave 3.83 g (yield in 3 steps 76 %) of (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.18 (t, 3H, J=6.8 Hz), 1.24 (t, 3H, J=7 Hz), 2.96 (d, 2H, J=6.5 Hz), 3.34-3.43 (m, 1H), 3.57-3.66 (m, 1H), 4.00 (t, 1H, 6.5 Hz), 4.18 (q, 2H, J=7 Hz), 5.30 (s, 1 OH), 6.74 (dm, 2H, J=8.5 Hz, unresolved), 7.10 (dm, 2H, J=8.5 Hz, unresolved).

^{13}C-NMR (100 MHz; $CDCl_3$): δ 14.2, 15.0, 38.4, 60.9, 66.2, 80.4, 115.1, 129.0, 130.5, 154.5, 172.7.

(g) 2-[4-(*tert*-Butoxycarbonylamino)phenyl]ethylmethanesulfonate

4-(2-Hydroxyethyl)phenylcarbamic acid *tert*-butylester (described in Example 1 (c)) (2.46 g; 10.38 mmole) was dissolved in dichloromethane (21 ml). Triethylamine (2.17 ml; 15.6 mmole) was added and the mixture was stirred for 20 min and then cooled on an ice-bath. Methanesulphonyl chloride (1.25 g, 10.9 mmole) was added slowly. The reaction mixture was stirred for 3.5 hours and the formed precipitate was filtered off. The filtrate was evaporated and the residue redissolved in ethyl acetate. A new precipitate was formed and filtered off and the filtrate evaporated. Chromatography on silica using heptane: ethyl

acetate (2:1, 1:1) gave 3 g (100 % yield) of 2-[4-(*tert*-butoxycarbonylamino)phenyl]-ethylmethanesulfonate

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.52 (s, 9H), 2.87 (s, 3H), 3.01 (t, 2H), 4.39 (t, 2H), 7.16 (d, 2H, J=8.45 Hz), 6.45 (bs, 1H), 7.33 (d, 2H, J=8.45 Hz)

^{13}C-NMR (100 MHz; $CDCl_3$: δ 28.2, 34.8, 37.1, 70.2, 80.3, 118.6, 129.2, 130.5, 137.3, 152.6.

(h) 3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid ethyl ester

2-[4-(*tert*-Butoxycarbonylamino)phenyl]ethylmethanesulfonate (52.9 g; 0.168 mmole), (S)-2-ethoxy-3-(4-hydroxyphenyl)propanoic acid ethyl ester (40 g; 0.168 mmole) and potassium carbonate (69.5 g; 0.503 mmole) were mixed in acetonitrile (1200 ml) and refluxed over night. Another portion of 2-[4-(*tert*-butoxycarbonylamino)phenyl]-ethylmethanesulfonate (2.5 g; 7.9 mmole) was added. The reaction mixture was refluxed for 8 more hours then filtered. Evaporation of the filtrate gave 76.6 g 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid ethyl ester.

This batch of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid ethyl ester (76.6 g) was combined with another batch of 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid ethyl ester (74.1 g) and flash chromatographed on silica using first toluen and then methanol as eluant. This gave a main fraktion of 80 g ester which was split in two portions of 40 g each and chromatographed on silica using toluene: ethyl acetate (2-5 %) as eluant. This procedure gave 69.9 g of pure 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid ethyl ester.

^{1}H-NMR (400 MHz; $CDCl_3$: δ 1.16 (t, 3H), 1.22 (t, 3H), 1.51 (s, 9H), 2.94 (d, 2H), 3.02 (t, 2H), 3.31-3.38 (m, 1H), 3.55-3.63 (m, 1H), 3.95 (t, 1H), 4.10 (t, 2H), 4.16 (q, 2H), 6.45 (bs, 1H), 6.8 (d, 2H), 7.13 (d, 2H), 7.19 (d, 2H), 7.29 (d, 2H).

(i) 3-{4-[2-(4-*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid

3-{4-[-(*tert*-Butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid ethyl ester (27 g; 0.06 mmole) was dissolved in THF (250 ml), and water (250 ml) was added during stirring followed by addition of lithium hydroxide hydrate (3.75 g; 0.089 mmole) dissolved in a small amount of water. The reaction mixture was stirred at room temperature over night and then concentrated by evaporation. The residue was washed once with ethyl acetate. The water phase was acidified upon cooling with hydrochloric acid (2M) and extracted with ethyl acetate. The organic phase was washed with brine dried with magnesium sulfate and evaporated. The residue was redissolved in dichloromethane and chromatography on silica using a gradient system of dichloromethane: methanol (0-100 %) gave 21.3 g (83 % yield) 3-{4-[2-(4-*tert*-butoxycarbonylaminophenyl)ethoxy]phenyl}-(S)-2-ethoxypropanoic acid.

^{1}H-NMR (600 MHz; $CDCl_3$: δ 1.17 (t, 3H), 1.51 (s, 9H), 2.93 (dd, 1H), 3.02 (t, 2H), 3.07 (dd, 1H), 3.42-3.47 (m, 1H), 3.55-3.6 (m, 1H), 4.04 (dd, 1H), 4.1 (t, 2H), 6.5 (bs, 1H), 6.8 (d, 2H), 7.13 (d, 2H), 7.19 (d, 2H), 7.28 (d, 2H).

^{13}C-NMR (100 MHz; CD_3OD): δ 15.3, 28.7, 36.1, 39.3, 67.1, 69.9, 80.7, 81.3, 115.4, 120.0, 130.3, 130.7, 131.4, 134.2, 138.8, 155.4, 159.1, 176.0.

Biological activity

The biological activity of the compound of the invention was tested in obese diabetic mice of the Umeå ob/ob strain. Groups of mice received the test compound by gavage once daily for 7 days. On the last day of the experiment the animals were anesthetized 2h after dose in a non-fed state and blood was collected from an incised artery. Plasma was analyzed for concentration of glucose, insulin and triglycerides. A group of untreated obese diabetic mice of the same age served as control. The weight of the mice was measured before and after the experiment and the obtained weight gain was compared to the weight gain of the control animals. The individual values for glucose, insulin and triglyceride levels of the mice from the test group were expressed as the percent rage of the corresponding values from the control group.

The desired "therapeutic effect" was calculated as the average percent reduction of the three variables glucose, insulin and triglycerides below the levels in the control animals. The therapeutic effect of the tested compounds according to the invention was compared to the same effect in the prior art compound troglitazone, administrered by gavage in the oral dose of 100 μmol/kg for 7 days.

The superior effects of the tested compound according to the invention compared to that of troglitazone when given in the same oral dose demonstrate the increased potency and efficiacy of the claimed compound.

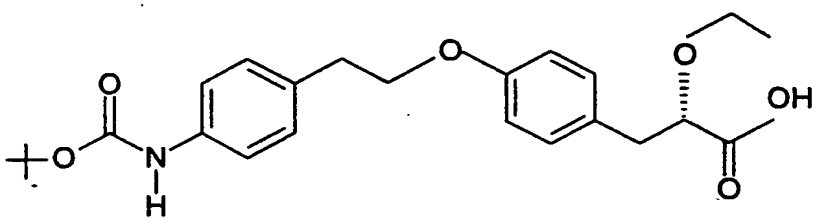
Abbreviations

NIDDM	non insulin dependent diabetes mellitus
VLDL	very low density lipoproteins
HDL	high density lipoproteins
IRS	insulin resistance syndrom
PPAR	peroxisome proliferator activated receptor

DEAD	diethyl azodicarboxylate
ADDP	azodicarbonyl dipiperidine
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
EDCxHCl	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
DCC	dicyclohexylcarbodiimide
HBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
TBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
PyBop	benzotriazole-1-yl-oxy-tris-pyrolidino-phosphonium hexafluorophosphate
DMF	dimethylformamide
DMAP	4-dimethylaminopyridine
TEA	triethylamine
DiPEA	diisopropylethylamine
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphtyl
COD	cyclooctadiene
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilylamine
TLC	thin layer chromatography
THF	tetrahydrofuran
Pd/C	palladium on charcoal
HOBt x H2O	1-hydroxybenzotriazole-hydrate
m	multiplet
t	triplet
s	singlet
d	doublet
q	quartet
qvint	quintet
br	broad
dm	multiplet of doublet
rac	racemate

CLAIMS

1. A compound having the formula

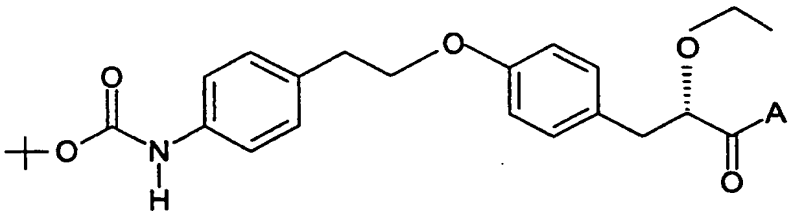


I

and pharmaceutically acceptable salts, solvates, and crystalline forms thereof.

2. A process for the preparation of a compound according to claim 1, characterized by

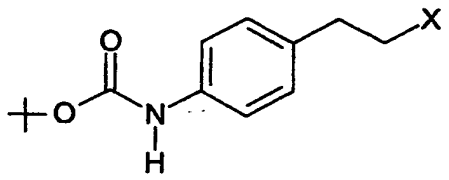
a) converting a compound of the formula II



II

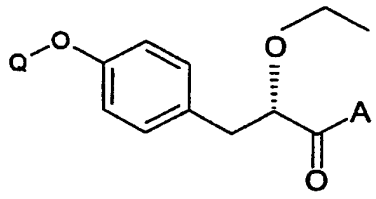
wherein A is a chiral auxiliary group or -OR^P, wherein R^P is a protective group, or

b) reacting a compound of the formula III



III

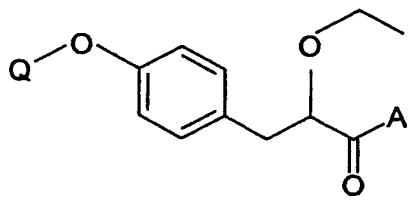
with a compound of the formula IV



IV

in which formulas A is -OH, a chiral auxiliary group or the group $-OR^P$, wherein R^P is a protective group, X is -OH or a leaving group and Q is H, whereafter, if necessary, hydrolysing the obtained compound, or

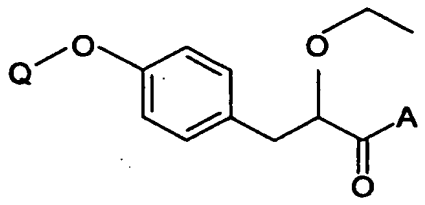
c) diastereoisomerically separating a compound of the formula V



V

wherein Q is $-CH_2CH_2Ph$-4-$NHCOO^tBu$ and A is a chiral auxiliary group whereafter, hydrolysing the obtained compound, or

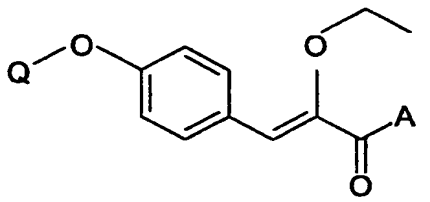
d) enantiomerically separating a compound of the formula V



V

wherein Q is $-CH_2CH_2Ph$-4-$NHCOO^tBu$ and A is -OH or $-OR^P$, wherein R^P is a protective group, whereafter, if necessary, hydrolysing the obtained compound, or

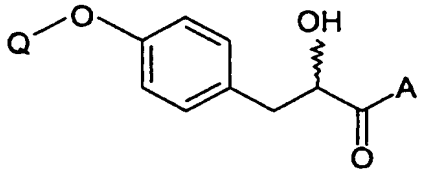
e) asymmetrically reducing a compound of the formula VII



VII

wherein Q is $-CH_2CH_2Ph$-4-$NHCOO^tBu$ and A is -OH, a chiral auxiliary group or the group $-OR^P$, wherein R^P is a protective group, whereafter, if necessary, hydrolysing the obtained compound, or

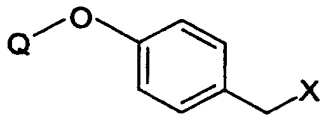
f) alkylating a compound of the formula XII



XII

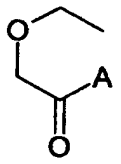
wherein Q is $-CH_2CH_2Ph$-4-$NHCOO^tBu$ and A is -OH, a chiral auxiliary group or the group $-OR^P$, wherein R^P is a protective group, whereafter, if necessary, hydrolysing the obtained compound, or

g) reacting a compound of the formula XV



XV

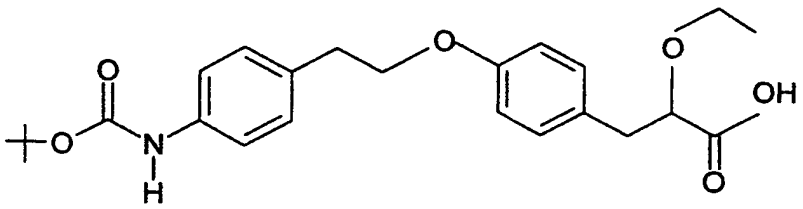
with a compound of the formula IX



IX

in which formulas X is a leaving group, Q is -CH_2CH_2Ph-4-NHCOO^{t}Bu and A is a chiral auxiliary group used to induce chirality in the compound whereafter, hydrolysing the obtained compound, or

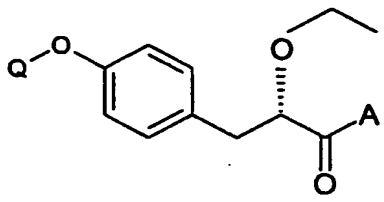
h) resolving a racemate of the formula I^{rac}



I^{rac}

whereafter, if desired, the compound obtained according to any of methods a)-h) is converted to a pharmaceutically acceptable salt and/or a solvate, such as a hydrate thereof.

3. A compound of the formula IV

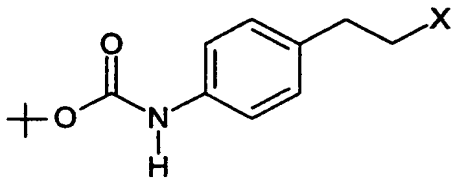


IV

wherein Q is hydrogen and A is -OH, a chiral auxiliary group or the group -OR^P, wherein R^P is a protective group.

4. A compound according to claim 3 wherein the formula IV A is -OH or -Oalkyl.

5. A compound of the formula III



III

wherein X is -OH or a leaving group.

6. A compound according to claim 5, wherein in formula III X is -OH.

7. A compound according to claim 1 for use in therapy.

8. A pharmaceutical formulation containing a compound according to claim 1 as active ingredient optionally together with a pharmaceutically acceptable carrier, adjuvant and/or diluent.

9. The use of a compound according to claim 1 in the manufacture of a medicament for the prophylaxis and/or treatment of clinical conditions associated with insulin resistance.

10. A method for the prophylaxis and/or treatment of clinical conditions associated with insulin resistance wherein a therapeutically active amount of a compound according to claim 1 is administered to a mammal in the need of such prophylaxis and/or treatment.

11. A method according to claim 10 wherein the prophylaxis and/or treatment of clinical conditions associated with insulin resistance is the prophylaxis and/or treatment of dyslipidaemia in such conditions.

12. A method according to claim 10 wherein the prophylaxis and/or treatment of clinical conditions associated with insulin resistance is the prophylaxis and/or treatment of hyperglycaemia in non insulin dependent diabetes mellitus.

13. A pharmaceutical formulation for use in the prophylaxis and/or treatment of clinical conditions associated with insulin resistance wherein the active ingredient is a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00940

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 271/28, A61K 31/325
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	STN International, File CAPLUS, CAPLUS accession no. 1999:194140, document no. 130:223305, Ajinomoto Co., Inc. et al: "Preparation and formulation of 5,11-dihydro-dibenz(b,e) (1,4)oxazepine derivatives as calcium antagonists"; & WO,A1,9912925, 19990318 --	5,6
P,X	WO 9857941 A1 (ASTRA AKTIEBOLAG), 23 December 1998 (23.12.98), page 31, line 15 - line 22 --	5,6
P,X	WO 9858934 A1 (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)), 30 December 1998 (30.12.98), page 56, line 1 - page 57, line 5 --	5,6

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 Sept 1999	07 -09- 1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00940

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9723458 A1 (WARNERLAMBERT COMPANY), 3 July 1997 (03.07.97), page 132, example 38	5,6
	--	
X	EP 0191448 A2 (SYNTEX (U.S.A.) INC.), 20 August 1986 (20.08.86), page 48, line 18 - line 29	5,6
	--	
X	STN International, File CAPLUS, CAPLUS accession no. 1997:684384, document no. 127:307307, Sankyo Co., Ltd., et al: "Preparation of phenylalkylcarboxylic acid derivatives lowering blood sugar level", WO,A1,9737970, 19971016	3,4
	--	
X	Tetrahedron Letters, Volume 35, No 19, 1994, Geoffrey G. Cox et al, "Competing O-H Insertion and Beta-Elimination in Rhodium Carbenoid Reactions; synthesis of 2-Alkoxy-3-arylpropanoates" page 3139 - page 3142	3,4
	--	
A	WO 9731907 A1 (GLAXO GROUP LIMITED), 4 Sept 1997 (04.09.97), page 23, line 25 - page 27, line 4, the claims	1-13
	--	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00940

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10-12
because they relate to subject matter not required to be searched by this Authority, namely:

See next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00940

Claims 10-12 relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/99

International application No.
PCT/SE 99/00940

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9857941 A1	23/12/98	AU 8047598 A	04/01/99
		SE 9702305 D	00/00/00
WO 9858934 A1	30/12/98	AU 8218998 A	04/01/99
		FR 2764889 A	24/12/98
WO 9723458 A1	03/07/97	AU 1353997 A	17/07/97
EP 0191448 A2	20/08/86	AU 591093 B	30/11/89
		AU 5336386 A	14/08/86
		DD 242804 A	11/02/87
		DD 252601 A	23/12/87
		DK 64286 A	12/08/86
		FI 860584 A	12/08/86
		GR 860384 A	09/05/86
		JP 61210071 A	18/09/86
		PH 22806 A	27/12/88
		PT 81987 A,B	01/03/86
		SU 1598870 A	07/10/90
		US 4595690 A	17/06/86
		US 4672071 A	09/06/87
WO 9731907 A1	04/09/97	AP 9700935 D	00/00/00
		AU 2093597 A	16/09/97
		CA 2247443 A	04/09/97
		CZ 9802750 A	13/01/99
		EP 0888317 A	07/01/99
		GB 9604242 D	00/00/00
		HR 970110 A	30/04/98
		NO 983940 A	27/10/98
		PL 328871 A	01/03/99